Physical activity and lung cancer risk in the European Prospective Investigation into Cancer and Nutrition cohort

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Research conducted predominantly in male populations on physical activity and lung cancer has yielded inconsistent results. We examined this relationship among 416,277 men and women from the European Prospective Investigation into Cancer and Nutrition (EPIC). Detailed information on recent recreational, household and occupational physical activity, smoking habits and diet was assessed at baseline between 1992 and 2000. Relative risks (RR) were estimated using Cox regression. During 6.3 years of follow-up we identified 607 men and 476 women with incident lung cancer. We did not observe an inverse association between recent occupational, recreational or household physical activity and lung cancer risk in either males or females. However, we found some reduction in lung cancer risk associated with sports in males (adjusted RR = 0.71; 95% confidence interval 0.50–0.98; highest tertile *vs.* inactive group), cycling (RR = 0.73; 0.54–0.99) in females and non-occupational vigorous physical activity. For occupational physical activity, lung cancer risk was increased for unemployed men (adjusted RR = 1.57; 1.20–2.05) and men with standing occupations (RR = 1.35; 1.02–1.79) compared with sitting professions. There was no evidence of heterogeneity of physical activity associations across countries, or across any of the considered cofactors. For some histologic subtypes suggestive sex-specific reductions, limited by subgroup sizes, were observed, especially with vigorous physical activity. In total, our study shows no consistent protective associations of physical activity with lung cancer risk. It can be assumed that the elevated risks found for occupational physical activity are not produced mechanistically by physical activity itself but rather reflect exposure to occupation-related lung cancer risk factors.

Key words: epidemiology; lung cancer; exercise; physical activity; cohort study

Lung cancer is the most common incident form of cancer in Europe, accounting for 381,500 cases in 2004 (13.2% of all incident cases).[1] Lung cancer is also the largest cause of cancer mortality (341,800 deaths in 2004; 20% of all cancer deaths), ranking first in men and now clearly established as the third most frequent cause of cancer deaths in women. Increasing trends in cancer mortality in women have been noted for several decades.[1] Lung cancer is also becoming a global burden since incidence and mortality rates have increased worldwide.[2,3] Since lung cancer has poor survival rates, primary prevention of this disease is a major public health priority.

Between 80 and 90% of lung cancers in Europe are attributable to cigarette smoking, the single most important risk factor for lung cancer.[4] Occupational exposure,[5] indoor[6] and outdoor air pollution[7] and lifestyle factors also play a role in lung cancer etiology.[8] One possible means for decreasing lung cancer, that has recently received research attention, is physical activity.[9,10] Physical activity might influence the risk of lung cancer through various mechanisms, such as improved ventilation and perfusion, which in turn may reduce both concentration of carcinogenic agents in the airways and duration of agent–airway interaction.[11]

The research conducted to date on physical activity and lung cancer has yielded inconsistent results. Four[12–15] of 9 cohort studies[12–20] and 2[10,21] of 5 case-control studies[9,10,21–23] demonstrated some significantly decreased risks of lung cancer among the most physically active subjects. In a 2002 review of the literature on physical activity and lung cancer, the IARC concluded that there is insufficient evidence for a preventive effect of physical activity for lung cancer risk, because of the limited number of studies conducted.[11] The inconsistency of the findings published so far may be attributable, in part, to the differences in physical activity assessment methods used and the varying degrees of control for possible confounding that was done in these studies.

Another important limitation of the studies conducted thus far is that only a few have examined the role of physical activity in lung cancer etiology in women. Seven studies[12,13,15,17,18,22,23] of the 14 investigations were restricted to male populations. Of the remaining 7 studies, only 4 included more than 100 female lung cancer cases[9,10,20,21] in their study populations.

We undertook, therefore, an investigation of the association between physical activity and lung cancer risk within the European Investigation on Cancer and Nutrition (EPIC). We report on 607 male and 476 female incident, histologically confirmed lung cancer cases diagnosed in the EPIC cohort to 2003. Results for the Danish subgroup (396 cases) of the EPIC cohort have been published previously.[20] Our analyses include the whole EPIC cohort and extend the methods for describing physical activity by using metabolic equivalent (MET) values. Goals of the analyses were threefold: (1) to analyze the largest female cohort on this topic, (2) to consider simultaneously recreational and occupational physical activity and (3) to investigate the possibly different effects for histological subtypes of lung cancer.

Material and methods

The EPIC project is an ongoing multi-centre prospective cohort study conducted in 23 centers in 10 European countries (Denmark, France, Germany, Greece, Italy, The Netherlands, Norway, Spain, Sweden and United Kingdom). The design and baseline data collection methods have been previously described.[24] The 521,457 eligible male and female participants, mostly aged 35–70, were recruited between 1992 and 2000 from the general population in a given geographic area. Exceptions were the French cohort (based on female members of a health insurance for school employees), the Utrecht cohort from The Netherlands (based on women attending breast cancer screening) and part of the Oxford cohort in the United Kingdom (based on vegetarians and other volunteers living throughout the UK). In addition, several Spanish and Italian centers were partly based on blood donors and the Italian cohort from Florence also includes breast cancer screening participants.[24] All participants provided their written informed consent. Approval for this study was obtained from the ethical review boards of the International Agency for Research on Cancer and from all local institutions where subjects had been recruited for the EPIC study.

Study population

Of 521,457 participants, we excluded prevalent lung cancer cases (n = 246), secondary lung cancer cases (n = 89), other prevalent cancer cases apart from non-melanoma skin cancers (n = 23,553) and subjects with missing dates of follow-up (n = 2,360). Further, we excluded subjects where no information on recreational or household or occupational physical activity was available, including the Norwegian cohort (n = 35,944), the Swedish Umeå cohort (n = 24,805) and further 18,233 subjects. Thus, the present analyses were based on 416,227 subjects, including 1,083 incident lung cancer cases.

Assessment of endpoints

Incident lung cancer cases were identified by population cancer registries (Denmark, Italy, The Netherlands, Spain, Sweden and United Kingdom) or by active follow-up (France, Germany and Greece). Active follow-up used a combination of methods, including health insurance records, cancer and pathology registries and direct contact of participants or next-of-kin. Mortality data were also obtained from cancer or mortality registries at the regional or national level. Follow-up began at the date of enrolment and ended at either the date of diagnosis of lung cancer, death or last complete follow-up. By April 2004, for the centers using record linkage with cancer registry data, complete follow-up was available until December 31, 1999 (Turin, Italy), June 30, 2000 (Bilthoven, The Netherlands), December 31, 2000 (Asturias, Murcia, Spain; Cambridge, UK), December 31, 2001 (Oxford, UK; Malmö, Sweden; Florence, Naples, Ragusa, Varese, Italy), June 30, 2002 (France), December 31, 2002 (Granada, Navarra, San Sebastian, Spain; Denmark) and June 30, 2003 (Utrecht, The Netherlands). For Germany and Greece, the end of the follow up was considered to be the last known contact, the date of diagnosis or the date of death, whichever came first. Definition of lung cancer cases were based on the International Classification of Diseases for Oncology (ICD-O-2) and included all invasive cancers that were coded as C34. After applying the aforementioned exclusion criteria, the database contained 1,083 cases of incident lung cancer cases. Histological information was available for 1,046 of 1,083 lung cancer cases and this information was used to define subgroups by histological type (adenocarcinomas, squamous cell carcinomas and small cell carcinomas).

Exposure assessment

A description of the data collection methods used in the EPIC study has been previously presented,[24] as has the assessment of physical activity.[25,26] Physical activity data were obtained at baseline in either in-person interviews or self-administered using a standardized questionnaire. In the centers in Malmö (Sweden) and Naples (Italy), the format for the physical activity questions was somewhat different than that in the other centers (categorical frequencies and durations rather than continuous); however, these data could be transformed and combined with the data from the remaining centers. An assessment of the relative validity and reproducibility of the EPIC physical activity questions was undertaken[27] and the questionnaire was found to be satisfactory for the ranking of subjects, although it was found to be less suitable for the estimation of energy expenditure.

Data on current occupational activity included employment status and the level of physical activity done at work (unemployed, sedentary, standing, manual, heavy manual and unknown). The categories ''manual'' and ''heavy manual'' were later combined to (heavy) manual due to a very small percentage (2%) of participants who reported heavy manual work. The frequency and duration of non-occupational physical activity data that were captured included housework, home repair (do-it-yourself), gardening, stair climbing, and recreational activities, including walking, cycling and all other sports combined as done in winter and summer separately. In addition, the frequency and duration of vigorous non-occupational activity, defined as all recreational and household activities causing sweating or faster heartbeat, were assessed. Housework, home repair, gardening, and stair climbing were combined to obtain an overall estimate of household activity. Walking, cycling and sports activities were combined to derive overall recreational activity. All household and recreational physical activities were combined to define total non-occupational physical activity. The reference time period was a typical week within the last year before the interview.

Since the intensity of recreational and household activities was not directly recorded, a metabolic equivalent (MET) value was assigned to each reported activity according to the Compendium of Physical Activities.[28] A MET is defined as the ratio of work metabolic rate to a standard metabolic rate of 1.0 (4.184 kJ) kg^{-1} h^{-1}. The MET values assigned to the non-occupational data were 3.0 for walking, 6.0 for cycling, 4.0 for gardening, 6.0 for sports, 4.5 for home repair (do-it-yourself work), 3.0 for housework, 8.0 for stair climbing and 9.0 for vigorous non-occupational physical activity. These mean MET values were obtained by estimating the average of all comparable activities in the Compendium. The mean number of hours per week of summer and winter household and recreational activities were estimated and then multiplied by the appropriate MET values to obtain MET-hours/week of activity.

Lifetime history of consumption of tobacco products was assessed in detail. This lifetime assessment included questions on smoking status (current, past or never smoker), type of tobacco (cigarettes, cigars or pipe), number of cigarettes currently smoked and age when participants started and, if applicable, quit smoking. Further, lifestyle and sociodemographic characteristics, including education, occupation, medical history, lifetime consumption of alcoholic beverages, as well as anthropometric measurements, were assessed at study entry from all subjects in the cohort. Diet over the previous twelve months was assessed at the time of enrolment using dietary assessment instruments that were specifically developed for each participating country.[24]

Statistical methods

We analyzed the association between physical activity and risk of lung cancer separately for male and female participants by calculating incidence rate ratios as estimates of relative risks (RR) using Cox proportional hazard models. Age was used as the underlying time variable in the counting process, with entry and exit time defined as the subject's age at recruitment and age at lung cancer diagnosis or censoring (death, lost to follow-up, end of follow-up), respectively. Models were stratified by age at recruitment (in one-year categories) and by study centre to account for centre effect such as follow-up procedures and questionnaire design.

Two sets of models are presented, the first adjusted for age, centre and lifetime smoking, considered as crude models for lung cancer, and the second further adjusted for other confounders. To cover smoking habits and history, we adjusted for smoking status (never smokers; current cigarette smokers; former smokers; other smokers, including pipe, cigar and occasional smokers; unknown), duration of smoking ($\leq$10, 11–20, 21–30, 31–40, 41–50 and >50 years), intensity of smoking (1–14, 15–24 or 25+ cigarettes/day) and time since smoking cessation (0–10, 11–20, or 20+ years ago). In the multivariate model, the following potential confounding variables were additionally considered: highest educational level (none or primary school, technical/professional school, secondary school, university degree, unknown), alcohol consumption (g/day), weight (kg) and height (cm) at baseline, energy intake excluding alcohol (kcal/day), vegetable consumption (g/day), fruit consumption (g/day), consumption of red and processed meat (g/day). In addition, occupational exposure to lung carcinogens (yes/no) was considered: the index was build up from a list of 28 occupations classified as being associated with a higher lung cancer risk, such as welding, shipyard and metal working, asbestos production and use, working with asphalt, construction and demolition work, working in transportation and working as cook or waiter. Continuous adjustment variables were categorized into quintiles. All percentile categorizations were calculated sex-specifically based on the entire cohort. For specific subtypes of physical activity an exclusive non-active group was defined and active persons were subdivided according to percentiles within actives only. A complete assessment of confounding and effect modification was undertaken. The results from the fully adjusted models are shown, as the exclusion of single or multiple factors did not result in more precise estimates for the effects of physical activity, and thus there was no advantage in using more parsimonious models.[29] For a subgroup of about 25%, additional binary information on environmental tobacco smoke at home and at work was available. Including these variables together with an extra category for missing values did not change the risk estimates.

For country-specific analyses, physical activity variables were treated as continuous. Heterogeneity between countries was assessed by χ^2 tests.[30] A *p*-value <0.1 was defined as heterogeneous and therefore the estimate from the pooled data could not be interpreted. All analyses were performed using SAS Statistical Software, Version 8.2 (SAS Institute, Cary, NC, USA). All statistical tests were two-sided.

Results

Overall, 416,227 participants, 130,438 males and 285,789 females, were followed for an average of 5.9 and 6.6 years, respectively (Table I). During follow-up, 607 male and 476 female cases of incident lung cancer were identified. Mean age at inclusion was 53.1 and 51.5 years, respectively. Ten male cases (1.6%) and 66 female cases (13.9%) were never-smokers.

Table II shows the characteristics of the EPIC participants in total and by non-occupational physical activity categories for men

TABLE I – COHORT CHARACTERISTICS (N = 416,227) FOR THE ANALYSES OF PHYSICAL ACTIVITY AND LUNG CANCER BY COUNTRY, THE EPIC STUDY

Country	Males					Females				
	Cohort size (N)	Age at recruitment, mean (SD)	Number of years of follow up (mean)	Person years (sum)	Lung cancer cases (N)	Cohort size (N)	Age at recruitment, mean (SD)	Number of years of follow up (mean)	Person years (sum)	Lung cancer cases (N)
France	–	–	–	–	–	65,473	52.7 (6.7)	8.4	551,417	38
Italy	14,209	50.2 (7.6)	5.3	76,018	44	31,043	50.6 (8.1)	6.2	191,948	37
Spain	15,451	50.7 (7.2)	6.8	105,727	56	25,350	48.3 (8.4)	6.6	167,341	14
United Kingdom	23,822	53.3 (13.7)	5.3	126,293	78	52,607	48.0 (14.6)	5.4	282,626	59
The Netherlands	7,171	43.2 (10.9)	4.5	32,530	7	24,478	52.2 (11.0)	6.7	162,946	68
Greece	10,680	52.9 (12.8)	3.7	39,392	36	15,135	53.3 (12.5)	3.7	56,354	3
Germany	22,012	52.4 (7.5)	5.8	128,229	108	28,343	49.1 (9.0)	5.9	165,878	29
Sweden	10,400	59.0 (7.0)	7.7	80,280	78	14,248	57.3 (7.9)	7.6	107,776	54
Denmark	26,693	56.6 (4.4)	6.6	177,439	200	29,112	56.7 (4.4)	6.8	196,637	174
Total	*130,438*	*53.1 (9.8)*	*5.9*	*765,907*	*607*	*285,789*	*51.5 (10.1)*	*6.6*	*1,882,923*	*476*

and women. Male and female participants classified in the lowest quartile for non-occupational physical activity were less frequent never-smokers compared to more active participants. In addition, males with a low activity level had a lower educational level, a slightly higher body weight, and a higher fruit intake. For females, those grouped into the lowest quartile of non-occupational physical activity had a higher educational level and a slightly larger body height. Weight, fruit intake and occupational exposure to lung carcinogens tended to be positively related, whereas vegetable intake, the consumption of red and processed meat and alcohol intake tended to be negatively related to non-occupational physical activity.

Table III shows the relative risks of lung cancer for different subtypes of physical activity considered mutually. Vigorous non-occupational physical activity was categorized into tertiles over active persons only, as 52,052 (47.0%) male and 133,014 (56.7%) female participants did not perform any vigorous activity. For females, household physical activity contributes about two-thirds to total non-occupational physical activity, whereas for males the contribution of household and recreational activity is about equal. The results by type of physical activity do not indicate clear protective reductions in lung cancer risk in association with physical activity. In the multivariate model, statistically significant increased risks of lung cancer were obtained in males being unemployed (RR = 1.57, 95% confidence interval (CI) 1.20–2.05) or having a standing occupation (RR = 1.35, 95% CI 1.02–1.79) compared to participants with a sitting occupation. In the female cohort, vigorous physical activity in the first and second tertile showed a reduction in risk, with OR = 0.65 (95% CI 0.43–0.98) and OR = 0.60 (95% CI 0.40–0.89), respectively, compared to women with no vigorous non-occupational activity.

It is conceivable that certain dietary and lifestyle factors may act as confounders or effect modifiers. In Table III, the models with the basic adjustment for age and smoking and the models with further adjustment yielded very similar results, indicating no major confounding effects. The adjustment had the highest impact on the risk estimates for occupational physical activity. From all considered adjustment factors besides smoking, the variable occupational exposure to lung carcinogens had the strongest impact on the risk estimates and the model fit statistics. More refined job classifications based on exposure to asbestos, heavy metals, polycyclic aromatic hydrocarbons, environmental tobacco smoke and silica yielded similar results. Considering the single types of physical activity in separate models rather than mutually adjusted did not result in notably different risk estimates (results not shown).

Country-specific and pooled analyses of physical activities showed no evidence of heterogeneity between countries (results not shown). The highest but non-significant indication for heterogeneity was found for vigorous physical activity in males (p = 0.15). When we re-estimated the models by omitting each country in turn, the estimates did not change considerably.

Table IV presents the results for the specific recreational and household activities that were originally reported on the questionnaires. Inverse associations with lung cancer risk are found for sports in males and for cycling in females. Risk estimates for persons grouped into the highest activity group compared to persons not reporting this specific activity were RR = 0.71 (95% CI: 0.50–0.98) for sports in males and RR = 0.73 (95% CI: 0.54–0.99) for cycling in females.

No clear monotone association between any type of non-occupational physical activity and lung cancer risk was found for any histologic subtype (Table V). The lowest odds ratio estimates were found for squamous carcinoma and small cell carcinoma in men with vigorous physical activity, for females for squamous and small cell carcinoma with household physical activity, and for other or non-specified carcinoma and for small cell carcinoma with vigorous physical activity.

Analyses on effect modifications for all considered cofactors, *e.g.* smoking and energy intake, did not indicate any interactions between physical activity and these factors (results not shown). Combining the male and female subgroups did not yield different results. Extensive sensitivity analyses, *e.g.*, by restricting the case definition to cases diagnosed at least 3 years after baseline, were performed (results not shown). However, besides the expected number of sporadically occurring significant results, no further information was gained from the data.

Discussion

In this large prospective cohort study with more than 1,000 lung cancer cases, we did not observe clear reductions in risk for lung cancer in association with physical activity either in women or in men. For occupational physical activity, the lowest risks were found for sitting work. The lung cancer risk was significantly increased for unemployed men and men with standing occupations compared to sitting professions. Only for some reported activities, specifically sports in males, cycling in females, and vigorous non-occupational physical activity were statistically significant risk reductions observed. For the different histologic subtypes, some indications for lung cancer risk reductions were found, especially for vigorous physical activity. There was no evidence of heterogeneity of physical activity associations across countries or for any of the considered cofactors.

Strengths of our study include its prospective nature and the large number of cases available for analysis. With 476 female lung cancer cases, it represents the largest prospective investigation into physical activity and lung cancer risk in females to date. Only one case-control study reported on more female lung cancer patients.[10] Furthermore, the effect of physical activity could be studied from several European cohorts with profound cultural differences. Our study assessed all-day physical activity, covering household, occupational, and recreational activities with respect to frequency and duration. Furthermore, we assessed a wide range of potential confounders, including diet, thereby overcoming some of the limitations of previous studies.

TABLE II – BASELINE CHARACTERISTICS OF 416,227 STUDY PARTICIPANTS BY QUARTILES OF NON-OCCUPATIONAL PHYSICAL ACTIVITY IN MET-HOURS/WEEK, THE EPIC STUDY

	Males					Females				
	0–<13.5	13.5–<27.5	27.5–<45.0	≥45.0	Total	0–<12.0	12.0–<24.0	24.0–<42.0	≥42.0	Total
N	32,780	33,037	32,294	32,327	130,438	70,380	71,042	71,536	72,831	285,789
Person-years	195,898	195,399	189,202	185,409	765,907	508,438	482,066	450,835	441,584	1,882,923
No. of cases	157	131	169	150	607	134	125	111	106	476
Categorical variables										
Smoking status (%)										
Never (%)	25.8	29.5	30.4	30.1	29.0	42.7	46.9	51.5	55.7	49.3
Current, 1–14 cigs/day (%)	9.9	9.1	9.2	9.1	9.3	9.0	9.2	9.7	9.9	9.5
Current, 15–24 cigs/day (%)	11.1	9.8	9.0	9.3	9.8	6.4	6.1	5.9	5.6	6.0
Current, 25+ cigs/day (%)	8.3	5.6	4.6	4.1	5.7	1.8	1.5	1.5	1.6	1.6
Former, stop <10 years ago (%)	14.3	13.5	13.6	13.1	13.6	8.0	8.5	8.2	7.7	8.1
Former, stop ≥10 years ago (%)	19.8	22.7	24.1	25.5	23.0	13.2	14.2	13.7	12.2	13.3
Other smoking (%)	10.9	9.8	9.2	8.8	9.6	19.0	13.6	9.5	7.3	12.3
Education										
None/primary (%)	38.4	30.4	29.4	27.7	31.5	17.5	20.3	29.3	40.0	26.9
Technical/professional (%)	20.5	23.8	24.8	28.5	24.4	16.3	20.8	22.3	21.1	20.1
Secondary (%)	17.3	14.7	13.4	12.5	14.5	32.0	26.8	22.2	19.9	25.2
University (%)	21.3	28.8	29.8	27.4	26.8	30.3	28.2	21.6	13.7	23.4
Occupational exposure to lung carcinogens (%)	33.6	31.1	31.1	32.6	32.1	2.9	3.3	4.3	4.4	3.7
Continuous variables										
Median										
Age (years)	53	53	53	54	53	51	51	52	51	51
Height (cm)	173.0	175.0	175.0	175.0	174.5	162.0	162.0	161.7	160.0	161.8
Weight (kg)	80.3	80.0	79.6	79.4	79.8	62.0	62.9	64.2	65.5	63.6
Energy intake w/o alcohol (kcal/d)	2254.9	2233.8	2256.4	2298.4	2259.3	1879.3	1882.3	1871.0	1903.9	1884.1
Vegetable intake (g/d)	159.4	162.2	165.7	162.9	162.7	206.5	203.6	195.3	194.4	200.0
Fruit intake (g/d)	188.8	170.3	172.2	173.3	175.6	209.3	219.8	241.8	262.7	234.3
Red+processed meat (g/d)	98.6	99.2	97.4	97.2	98.2	68.7	64.6	61.7	60.8	63.8
Alcohol intake (g/d)	14.2	15.1	15.2	14.1	14.7	5.5	5.5	4.0	2.3	4.3
Q1, Q3										
Age (years)	46, 59	47, 59	46, 60	46, 61	46, 59	46, 57	45, 58	45, 59	44, 59	45, 58
Height (cm)	168.0, 178.0	170.0, 179.6	170.0, 179.9	170.0, 180.0	169.5, 179.3	158.0, 166.2	158.0, 167.0	157.0, 166.0	155.8, 165.0	157.0, 166.0
Weight (kg)	73.0, 88.7	73.0, 87.9	72.5, 87.4	72.4, 87.1	72.8, 87.8	56.0, 69.9	56.6, 70.2	58.0, 72.0	59.0, 73.5	57.2, 71.5
Energy intake w/o alcohol (kcal/d)	1848.2, 2729.5	1839.4, 2689.4	1855.3, 2721.1	1879.2, 2794.0	1854.0, 2732.4	1538.5, 2269.0	1554.0, 2271.7	1546.9, 2254.3	1567.6, 2300.4	1552.2, 2274.2
Vegetable intake (g/d)	97.9, 271.0	103.1, 258.9	106.0, 261.2	106.9, 259.0	103.6, 262.2	132.5, 300.1	130.9, 299.2	124.2, 303.0	124.4, 309.8	127.6, 302.7
Fruit intake (g/d)	90.3, 352.3	89.8, 312.2	95.1, 309.0	96.8, 302.5	93.3, 318.7	122.0, 321.7	129.8, 332.9	141.3, 367.2	154.1, 407.8	135.8, 356.5
Red+processed meat (g/d)	62.5, 142.4	60.7, 142.6	58.0, 140.8	56.6, 142.5	59.5, 142.0	38.7, 100.2	35.2, 95.8	34.7, 92.1	35.2, 90.6	35.9, 94.7
Alcohol intake (g/d)	4.1, 32.8	5.6, 32.8	5.6, 32.4	5.0, 32.0	5.1, 32.4	1.0, 13.4	1.1, 12.9	0.6, 11.6	0.2, 9.9	0.6, 11.9

TABLE III – ADJUSTED RELATIVE RISKS AND 95% CONFIDENCE INTERVALS OF LUNG CANCER BY TYPE OF PHYSICAL ACTIVITY BY GENDER, THE EPIC STUDY

Males							Females						
Category	Person years	Number of cases	Smoking adjusted[1] RR	Smoking adjusted[1] 95% CI	Full adjustment[2] RR	Full adjustment[2] 95% CI	Category	Person years	Number of cases	Smoking adjusted[1] RR	Smoking adjusted[1] CI	Full adjustment[2] RR	Full adjustment[2] CI
Occupational physical activity[3]													
Unemployed	173,536	290	1.82	1.40–2.37	1.57	1.20–2.05	Unemployed	740,528	260	1.39	1.05–1.84	1.25	0.94–1.66
Sitting	282,645	106	1.0	–	1.0	–	Sitting	462,101	84	1.0	–	1.0	–
Standing	159,998	101	1.49	1.13–1.96	1.35	1.02–1.79	Standing	545,483	79	1.20	0.88–1.65	1.14	0.83–1.57
(Heavy) manual	149,727	110	1.45	1.10–1.90	1.25	0.94–1.66	(Heavy) manual	134,815	53	1.20	0.84–1.71	1.09	0.76–1.56
Non-occupational activity (recreational and household activity combined) (quartiles in MET–hours/week)[3]													
0–<33.7	195,898	157	1.0	–	1.0	–	0–<51.1	508,438	134	1.0	–	1.0	–
33.7–<56.6	195,399	131	0.88	0.70–1.12	0.89	0.70–1.13	51.1–<82.2	482,066	125	0.96	0.75–1.24	0.99	0.77–1.26
56.6–<86.6	189,201	169	1.18	0.94–1.48	1.20	0.96–1.51	82.2–<123.0	450,834	111	0.89	0.68–1.17	0.93	0.71–1.21
≥86.6	185,408	150	0.96	0.75–1.22	0.97	0.76–1.25	≥123.0	441,584	106	0.99	0.74–1.32	1.00	0.75–1.35
Recreational physical activity (quartiles in MET-hours/week)[4]													
0–<13.5	192,585	186	1.0	–	1.0	–	0–<12.0	488,994	133	1.0	–	1.0	–
13.5–<27.5	189,565	163	1.08	0.87–1.34	1.09	0.88–1.35	12.0–<24.0	489,583	116	0.96	0.74–1.23	0.99	0.77–1.28
27.5–<45.0	196,376	125	0.84	0.67–1.07	0.85	0.67–1.08	24.0–<42.0	423,430	103	0.93	0.72–1.22	0.99	0.76–1.30
≥45.0	187,381	133	0.99	0.78–1.26	1.00	0.79–1.27	≥42.0	480,915	124	0.93	0.72–1.21	0.99	0.76–1.30
Household physical activity (quartiles in MET-hours/week)[4]													
0–<11.0	190,308	145	1.0	–	1.0	–	0–<26.0	511,508	130	1.0	–	1.0	–
11.0–<23.8	195,113	119	0.77	0.60–1.00	0.77	0.60–1.01	26.0–<49.3	486,898	136	1.04	0.82–1.34	1.04	0.81–1.33
23.8–<43.6	192,798	140	0.85	0.67–1.09	0.86	0.67–1.10	49.3–<86.3	457,305	113	0.89	0.68–1.17	0.90	0.68–1.18
≥43.6	187,688	203	1.03	0.81–1.31	1.04	0.82–1.31	≥86.3	427,213	97	0.97	0.71–1.32	0.95	0.70–1.30
Vigorous non-occupational physical activity (tertiles over actives, MET-hours/week)[5]													
None	293,958	255	1.0	–	1.0	–	None	865,578	192	1.0	–	1.0	–
>0–<15.0	93,962	56	0.85	0.63–1.16	0.94	0.69–1.28	>0–<13.5	225,135	30	0.61	0.41–0.92	0.65	0.43–0.98
15.0–<40.0	122,925	70	0.81	0.60–1.07	0.86	0.65–1.15	13.5–<33.5	241,795	33	0.56	0.38–0.84	0.60	0.40–0.89
≥40.0	116,226	68	0.84	0.63–1.11	0.87	0.65–1.16	≥33.5	180,191	43	0.90	0.63–1.28	0.92	0.65–1.32

[1]Models stratified by age and centre.–[2]Models stratified by age and centre, and adjusted for smoking (smoking status, duration, intensity, time since smoking cessation), weight, height, education, total energy intake without energy from alcohol, alcohol intake, intake of fruits, intake of vegetables, intake of red and processed meat and occupational exposure to lung carcinogens.–[3]Non-occupational and occupational physical activity are considered mutually, i.e. are simultaneously in the model.–[4]Recreational and household and occupational physical activity are considered mutually, i.e. are simultaneously in the model. Additionally adjusted for occupational physical activity.–[5]A total of 70,802 participants (17%), 19,758 males and 51,044 females, including 158 male and 178 female cases, are excluded due to incomplete information for the calculation of the corresponding MET-hours/week values. Additionally adjusted for occupational physical activity.

Our study also has some limitations that need to be considered. Although the EPIC cohort is very large, these results are based on a relatively short duration of follow-up (6.3 years). We approached this issue by excluding all cases diagnosed within the first 2 or 3 years of follow-up from our analyses. We did not observe differences in our results. A second limitation is that physical activity was assessed at baseline only, whereas for the discussed biologic mechanisms an individual's physical activities in the distant past might be more relevant. Based on studies that assessed physical activity information at several lifetime periods, it can be speculated that a high percentage of individuals follow a rather constant physical activity pattern throughout life.[31,32] Nevertheless, we can not exclude that there may have been some exposure misclassifications, since changes in activity patterns over lifetime could not be assessed. Finally, although we did a comprehensive adjustment for lifetime smoking habits, we did not have full data on environmental tobacco smoking exposure on all participants. Hence, some confounding by smoking and other unmeasured confounders such as socioeconomic status (SES) may still have occurred in these analyses.

For occupational physical activity, we did not find an inverse association with lung cancer risk. This is consistent with most[13,14,16,17,22,23] but not all[12] studies that have specifically examined this type of activity. Four studies in which the classification of occupational activity was similar to ours[14,17,20,22] found risk estimates for lung cancer in men of 1.01–1.23 for various levels of occupational physical activity compared with sitting work. We controlled for a number of risk factors for lung cancer, leading to risk estimates closer to one for all occupational physical activity categories compared to the estimates that were adjusted for smoking only. Nevertheless, there may still be confounding from other occupational risk factors. Many lung carcinogens exist in certain work environments and these carcinogens may be particularly prevalent in manual and heavy manual occupations where we found an increased risk of lung cancer. It is also possible that the classification of occupational physical activity reflects classification of professions and other aspects of lifestyle. For example, we cannot expect length of school education in 5 levels to adjust properly for differences in SES. This lack of full adjustment of confounding by SES might partly explain why we observed the lowest lung cancer rates for sitting work. Only 3 studies[14,16,20] investigated occupational physical activity in women. They reported relative risks in the range of 0.7–1.1. As in our study, none of these estimates were significantly different from one.

Our analysis revealed a significantly increased lung cancer risk for unemployed men (RR = 1.57, 95% CI 1.20–2.05). ''Being unemployed'' is not a well-defined physical activity category, as it includes retirees, temporarily unemployed, disabled, ill and homemakers. Thus, it is important to consider this category separately from the other occupational groups. Our result is in agreement with the 2 studies who reported on unemployed men as an extra category. Colbert *et al.*[17] reported a RR of 1.27 (95% CI 1.04–1.56) and Bak *et al.*[20] found a RR of 1.54 (95% CI 1.00–2.37), with the latter being a sub-cohort of the present analyses. It can be hypothesized that the nonworking category may largely consist of men retired from occupations other than sitting physical activity. Persons in this group might have comorbidities affecting risk for lung cancer (such as chronic obstructive pulmonary disease) or a higher chance of being diagnosed within the observation period if they are therefore under the regular care of a physician. Furthermore, comorbidity and preclinical illness resulting in inactivity could underlie the increased risk seen among unemployed men. In

TABLE IV – RISK ESTIMATES FOR LUNG CANCER IN RELATION TO CATEGORIES IN MET-HOURS/WEEK SPENT ON 7 DIFFERENT TYPES OF RECREATIONAL AND HOUSEHOLD PHYSICAL ACTIVITY BY GENDER, THE EPIC STUDY

Subtype of activity	Males				Females			
	Category[1]	Number of cases	RR[2]	95% CI	Category[1]	Number of cases	RR[2]	95% CI
Recreational physical activity								
Sport	None	454	1.0	–	None	283	1.0	–
	>0–<9.0	53	0.82	0.61–1.10	>0–<6.0	79	0.95	0.73–1.23
	9–<18.0	60	0.77	0.59–1.02	6.0–<15.0	43	0.81	0.58–1.12
	≥18.0	40	0.71	0.50–0.98	≥15.0	71	1.14	0.87–1.50
Walking	None	69	1.0	–	None	50	1.0	–
	>0–<9.0	157	0.99	0.73–1.33	>0–<9.0	167	0.89	0.63–1.25
	9.0–<21.0	174	1.03	0.76–1.39	9.0–<21.0	114	0.88	0.61–1.26
	≥21.0	207	1.00	0.74–1.35	≥21.0	145	0.98	0.68–1.39
Cycling	None	354	1.0	–	None	264	1.0	–
	>0–<6.0	94	1.15	0.90–1.47	>0–<6.0	62	0.84	0.62–1.12
	6.0–<18.0	79	0.94	0.72–1.22	6.0–<18.0	71	0.77	0.58–1.02
	≥18.0	80	1.01	0.78–1.32	≥18.0	79	0.73	0.54–0.99
Household physical activity								
Gardening	None	224	1.0	–	None	207	1.0	–
	>0–<6.0	87	0.88	0.68–1.15	>0–<6.0	84	1.04	0.79–1.36
	6.0–<16.0	134	1.09	0.86–1.38	6.0–<12.0	87	0.94	0.72–1.22
	≥16.0	162	1.06	0.84–1.34	≥12.0	98	1.16	0.89–1.51
Housework	None	183	1.0	–	None	13	1.0	–
	>0–<6.0	146	1.26	0.97–1.63	>0–<21.0	168	0.95	0.52–1.75
	6.0–<15.0	127	1.18	0.91–1.55	21.0–<60.0	170	0.85	0.47–1.55
	≥15.0	151	1.13	0.87–1.46	≥40.0	125	0.90	0.49–1.64
Climbing stairs	None	240	1.0	–	None	158	1.0	–
	>0–<1.4	165	1.08	0.86–1.38	>0–<0.9	110	1.17	0.88–1.54
	1.4–<2.6	102	0.94	0.72–1.22	0.9–<2.1	131	1.07	0.82–1.41
	≥2.6	100	0.89	0.57–1.18	≥2.1	77	0.90	0.68–1.19
Do-it-yourself	None	290	1.0	–	None	331	1.0	–
	>0–<6.8	78	0.73	0.54–1.01	>0–<4.5	60	1.07	0.80–1.44
	6.8–<15.8	104	0.81	0.62–1.06	4.5–<13.5	33	1.02	0.70–1.49
	≥15.8	135	0.99	0.77–1.27	≥13.5	52	1.17	0.85–1.61

[1]Baseline defined as all non-active persons within the subtype; the other persons are grouped into tertiles over active persons only; categories in MET-hours/week.–[2]Mutually adjusted for all other subtypes and occupational physical activity. Models stratified by age and centre, and adjusted for smoking (smoking status, duration, intensity, time since smoking cessation), weight, height, education, total energy intake without energy from alcohol, alcohol intake, intake of fruits, intake of vegetables, intake of red and processed meat, occupational exposure to lung carcinogens.

our study, only limited data on comorbidities is available. However, exclusion of the first 3 years of follow-up did not change the risk estimates, arguing against this explanation. Further analyses (results not shown) revealed that for any given age, men ''not working'' are at higher risk of lung cancer than those working. Overall, we feel that our results for the ''unemployed'' category reflect the effects of occupational exposures that place people at risk for lung cancer and the healthy worker survivor effect, whereby workers who leave work are at increased risk for occupational disease for several years after job termination.

We did not find any association between lung cancer risk and total recreational or household physical activities, neither in women nor in men. However, when we examined specific types of reported recreational activities we found inverse associations for sports in males and for cycling in females. Recreational physical activity in men was studied in 6 studies[10,14,15,17,19,20] out of which 3 studies[10,14,15] reported protective effects. In women, out of 6 studies[9,10,14,19–21] 4 found some protective effects.[9,10,19,21] However, it has to be noted that in some studies[9,10,21] with positive findings, recreational activity was primarily defined as sports for which we also found some indications for protective effects. We also found some protective effects for vigorous non-occupational physical activity. A possible explanation why these activities demonstrated protective effects whereas other activities did not is that these activities are more salient activities that may be recalled better than other activities that are performed less frequently and are less structured.[33] Hence, there may have been less measurement error for these variables. On the other hand, it is not clear whether these differences between active and non-active persons are due to physical activity *per se*. Such results could also be caused by confounding, because participation in specific activities might also be associated with socio-economic factors.

We do not report results on a summary variable for total physical activity. There was no information on the duration and frequency of occupational activity. This precluded estimating a sum of all types of activity in MET-hours/week. Furthermore, because of the discussion on occupational physical activity above and the different directions of effects on lung cancer risk of occupational activity compared to recreational and household activities, we decided not to pursue any kind of summary variable any further.

We assessed a wide range of potential confounders, including dietary intake. Individuals who are active are also more likely to consume a diet rich in fruits and vegetables.[34] Diet-related factors have been considered as adjustment variables in 7 studies,[9,10,16–18,20,35] some of which were restricted to alcohol intake and total energy intake. Two studies[17,20] took into account vegetable or fruit intake. All but one[12] performed some adjustment for smoking. In our study, smoking habits constitute the major confounding factor. Crude analyses without adjustment for smoking indicated clear protective effects of physical activity (results not shown). This change in the risk estimates after adjustment for smoking highlights the possibility that residual confounding from smoking may have occurred in these data. For 78% of the cohort, additional information on the amount of cigarettes smoked historically was available. Including this information into the models did not yield different results. We observed little or no confounding for other factors. The most pronounced effect came from occupational exposure to lung carcinogens as confounder for occupational physical activity. The large sample size enabled us to evaluate the associations stratified by some potential effect modifiers.

TABLE V – ADJUSTED RELATIVE RISKS[1] OF LUNG CANCER BY TUMOUR SUBTYPES FOR MALES AND FEMALES, THE EPIC STUDY

	Adenocarcinoma		Squamous carcinoma		Small cell carcinoma		Other or non-specified carcinoma	
	RR	95% CI	RR	95% CI	RR	95% CI	RR	95% CI
Males	(N_{cases} = 153)		(N_{cases} = 172)		(N_{cases} = 109)		(N_{cases} = 173)	
Non-occupational physical activity (MET-hours/week)								
0–<33.7	1.0	–	1.0	–	1.0	–	1.0	–
33.7–<56.6	1.04	0.65–1.67	0.73	0.45–1.16	0.70	0.40–1.25	1.07	0.70–1.66
56.6–<86.6	1.43	0.91–2.26	1.29	0.84–1.98	0.80	0.46–1.39	1.26	0.82–1.94
≥86.6	0.90	0.53–1.52	1.17	0.75–1.83	0.84	0.48–1.46	0.94	0.58–1.51
Recreational physical activity (MET-hours/week)								
0–<13.5	1.0	–	1.0	–	1.0	–	1.0	–
13.5–<27.5	1.44	0.94–2.21	0.75	0.49–1.14	0.91	0.54–1.55	1.34	0.90–2.01
27.5–<45.0	0.97	0.60–1.56	0.84	0.55–1.29	0.74	0.42–1.32	0.85	0.54–1.35
≥45.0	0.92	0.55–1.53	0.94	0.60–1.45	0.95	0.54–1.67	1.21	0.76–1.92
Household physical activity (MET-hours/week)								
0–<11.0	1.0	–	1.0	–	1.0	–	1.0	–
11.0–<23.8	0.82	0.50–1.35	0.60	0.35–1.01	0.80	0.44–1.48	0.87	0.55–1.38
23.8–<43.6	0.73	0.44–1.22	0.99	0.62–1.59	0.86	0.48–1.57	0.84	0.53–1.32
≥43.6	1.03	0.64–1.65	1.25	0.80–1.95	0.94	0.53–1.67	0.90	0.58–1.41
Vigorous non-occupational physical activity[2] (MET–hours/week)								
None	1.0	–	1.0	–	1.0	–	1.0	–
>0–<15.0	1.06	0.58–1.94	1.13	0.64–2.01	1.17	0.61–2.23	0.52	0.25–1.07
15.0–<40.0	1.04	0.59–1.82	0.91	0.53–1.55	0.68	0.34–1.37	0.73	0.41–1.29
≥40.0	0.98	0.55–1.75	0.73	0.41–1.28	0.59	0.28–1.27	1.02	0.62–1.70
Females	(N_{cases} = 181)		(N_{cases} = 61)		(N_{cases} = 77)		(N_{cases} = 157)	
Non-occupational physical activity (MET-hours/week)								
0–<51.1	1.0	–	1.0	–	1.0	–	1.0	–
51.1–<82.2	0.81	0.54–1.21	1.06	0.53–2.11	1.14	0.62–2.08	1.15	0.74–1.81
82.2–<123.0	0.74	0.48–1.15	0.79	0.37–1.68	0.80	0.39–1.62	1.43	0.90–2.27
≥123.0	0.80	0.51–1.28	0.81	0.36–1.83	1.26	0.61–2.57	1.29	0.76–2.21
Recreational physical activity (MET-hours/week)								
0–<12.0	1.0	–	1.0	–	1.0	–	1.0	–
12.0–<24.0	0.87	0.58–1.32	1.22	0.60–2.48	0.60	0.29–1.26	1.30	0.83–2.04
24.0–<42.0	0.79	0.51–1.23	0.96	0.43–2.10	1.15	0.59–2.25	1.30	0.81–2.08
≥42.0	0.77	0.50–1.19	1.16	0.55–2.44	1.43	0.76–2.69	1.05	0.64–1.71
Household physical activity (MET-hours/week)								
0–<26.0	1.0	–	1.0	–	1.0	–	1.0	–
26.0–<49.3	1.00	0.66–1.51	0.99	0.50–1.95	0.91	0.51–1.62	1.21	0.77–1.90
49.3–<86.3	1.02	0.66–1.58	0.53	0.23–1.19	0.37	0.17–0.82	1.36	0.85–2.19
≥86.3	0.84	0.50–1.40	0.70	0.30–1.64	0.69	0.33–1.48	1.46	0.84–2.53
Vigorous non-occupational physical activity[2] (MET-hours/week)								
None	1.0	–	1.0	–	1.0	–	1.0	–
>0–<13.5	0.75	0.40–1.41	1.31	0.39–4.36	0.69	0.24–1.93	0.47	0.22–1.01
13.5–<33.5	0.62	0.33–1.19	1.38	0.37–5.12	0.50	0.18–1.42	0.54	0.28–1.06
≥33.5	1.09	0.61–1.92	2.03	0.67–6.16	0.81	0.30–2.16	0.70	0.37–1.30

[1]Stratified by age and centre, and adjusted for smoking (smoking status, duration, intensity, time since smoking cessation), weight, height, education, total energy intake without energy from alcohol, alcohol intake, intake of fruits, intake of vegetables, intake of red and processed meat, occupational exposure to lung carcinogens, and occupational physical activity.–[2]A total of 70,802 participants (17%), 19,758 males and 51,044 females, including 158 male and 178 female cases, are excluded due to incomplete information for the calculation of the corresponding MET-hours/week values.

Previous studies suggested age,[17–19] smoking history,[9,10] BMI[10] and gender[14,19] as effect modifiers. We cannot confirm any of these possible effect modifiers or suggest any new ones based on our study. However, because a large percentage of the cases have smoked, only limited conclusions can be drawn from our study for never-smokers who develop lung cancer.

It is unclear whether or not the association between physical activity and lung cancer is different for the various histologic subtypes. Our study yielded some indications for sex-specific risk reductions, especially for vigorous physical activity but not for recreational physical activity, for some histologic subtypes. No clear monotone associations were found; however, these analyses might be limited by subgroup sizes. Different effects of physical activity on various histological types of lung cancer have been reported. Thune and Lund[14] found for recreational physical activity that the association was strongest for small cell carcinoma and less marked for adenocarcinoma, with no association for squamous cell carcinoma in men. Mao *et al.*[10] observed greater reductions in lung cancer risk, with activities from sports and gardening for squamous cell carcinoma in women, small cell carcinoma in men, and other types/unspecified histologic subtypes in both genders. One study[17] found no apparent heterogeneity of risks by histologic subtypes.

Several biologic mechanisms are hypothesized for the association between physical activity and lung cancer risk. The first is that increased levels of physical activity increase pulmonary ventilation and perfusion,[36] which in turn reduce the concentration of carcinogenic agents in the airways, the duration of agent–airway interaction[37] and particle deposition.[14] However, it is mechanistically also possible that exposure to air pollutants might also increase with increased respiration.[38] Another hypothesis is that exercise may affect lung cancer risk through its effects on insulin-like growth factor levels and their binding proteins and thus inhibit cellular mitosis.[39] Further, physical activity may enhance endogenous antioxidant defenses such as the glutathione system and reduces oxidative stress.[40–42] These and other mechanisms may work separately or in combination to modify lung cancer risk.

In conclusion, these data do not suggest a consistent inverse association between recent occupational, recreational or household physical activity and lung cancer risk in males and in females. However, we found some indications for protective effects of physical activity through sports (males) and cycling and vigorous non-occupational physical activity (females). It can be assumed that the elevated risks found for occupational physical activity are not produced mechanistically by physical activity itself but rather mirror the exposure to occupation-related lung cancer risk factors.

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